TABLE 4A.—*Coronary heart disease (men). Age-standardized death rates for ex-cigarette smokers with history of cigarette smoking only, by former number of cigarettes smoked per day and years since last cigarette smoking. Death rates for current cigarette smokers with history of cigarette smoking only and men who never smoked regularly are shown for comparison. Men aged 50–69*

Ex-cigarette smokers (years since last cigarette smoking)	Smoked 1–19 cigarettes a day			Smoked 20+ cigarettes a day		
	Number of men	Number of deaths	Death rate	Number of men	Number of deaths	Death rate
Under 1 year	746	27	[1] 1,005	2,244	77	[1] 1,070
1 to 4 years	1,844	51	718	5,435	195	1,003
5 to 9 years	1,770	48	725	5,803	152	732
10+ years	4,209	84	498	8,142	206	679
Total ex-smokers	8,569	210	635	21,624	630	813
Current cigarette smokers	22,808	781	947	56,886	1,895	1,029
Never smoked regularly	55,728	1,114	502	55,728	1,114	502

[1] Four or more but less than 10 deaths expected in some of the component 5-year age groups.

SOURCE: Hammond, E. C. [(47), p. 148].

Doll and Hill

In a prospective study by Doll and Hill (*27*) of mortality among British physicians whose smoking habits had been previously recorded, there were 1,369 deaths in the course of 10 years in which the underlying cause was coronary heart disease (*27*, table 1). The physician population under observation totaled 320,185 person-years. The CHD deaths were classified into three major subcategories: Group 1, comprising 35 CHD deaths in which an associated condition related to smoking, e.g., lung cancer, was recorded on the death certificate; Group 2, comprising 721 CHD deaths in which no other significant contributory cause of death was recorded on the death certificate; and Group 3, comprising 613 CHD deaths which were associated with some other contributory cause, including conditions known to predispose to coronary heart disease, e.g., hypertension, diabetes, and obesity. The CHD death rates for smokers and nonsmokers based only on Group 1 deaths, while subject to large variation, show the largest differentials (data not shown). Among smokers of 25 or more cigarettes daily, the age-adjusted CHD death rate was nearly eight times that in nonsmokers.

Based on Group 2 coronary heart disease deaths, presumably uncomplicated by any other significant disease, the mortality ratio of age-adjusted death rates among continuing cigarette smokers to nonsmokers is found to be 1.6, and for heavy smokers to nonsmokers the

ratio is 2.0. However, as shown in table 5, the mortality differentials between smokers and nonsmokers are much larger at the younger ages.

TABLE 5.—*Mortality ratios for different types of coronary heart disease by smoking habits*

Age group	Group 2 [1] CHD			Group 3 CHD		
	Non-smokers	Continuing cigarette smokers		Non-smokers	Continuing cigarette smokers	
		All amounts	25 or more per day		All amounts	25 or more per day
35 to 44	1.0	4.7	9.7	[2]	[2]	[2]
45 to 54	1.0	3.8	3.5	1.0	1.1	1.7
55 to 64	1.0	1.4	1.6	1.0	1.4	1.9
65 to 74	1.0	1.4	1.8	1.0	1.4	.8
75 to 84	1.0	1.1	2.0	1.0	.8	.2
85 plus	1.0	1.0	[3]	1.0	1.4	[3]
Age adjusted—All ages	1.0	1.6	2.0	1.0	1.1	.9

[1] See text for definitions.
[2] Not calculable; no rate for nonsmokers because of so few deaths.
[3] Very few men in this category.

SOURCE: Data in above table based on values from Study of British Physicians. Table 3 (*27*).

The mortality ratios shown for Group 3 deaths, i.e., CHD deaths accompanied by some other complicating disease, suggest that, for all age groups combined, smokers do not have any special risk to this type of coronary death. However, smokers below the age of 65 appear to be at a somewhat greater risk, while no consistent differentials are observed among persons in the older age groups.

In summary, the study substantiates other mortality studies' findings that CHD mortality ratios (current cigarette smokers vs. nonsmokers) increase with the number of cigarettes smoked daily, that the ratios are highest in the age group 45–54, and that they decrease as age advances. Moreover, smoking apparently is associated with deaths from coronary heart disease among persons free of other serious disease states.

In a prospective study of California longshoremen, Borhani (*17*) reported on the mortality experience of more than 3,700 men observed for 10 years. Table 6, derived from his data, provides some additional insights on both the independent and the interaction effects of cigarette smoking.

Men 45–64 years of age who were heavy smokers experienced higher death rates from coronary heart disease than did nonsmokers independent of whether they were hypertensive or nonhypertensive.

TABLE 6.—*Mortality ratio from coronary heart disease among male hypertensives and nonhypertensives by smoking history and age*

Age group	Blood pressure status [1]	Nonsmokers [2]	Heavy smokers [2]
45 to 54	Nonhypertensive	1.0	2.2
	Hypertensive	2.5	9.6
55 to 64	Nonhypertensive	1.0	5.8
	Hypertensive	5.9	9.4

[1] Hypertensives are defined as those having systolic blood pressure of 160 mm. Hg. or over or diastolic blood pressure of 95 mm. Hg. or over. Nonhypertensives have systolic blood pressure less than 160 mm. Hg or diastolic blood pressure less than 95 mm. Hg.
[2] Nonsmokers in this particular study are defined as those not smoking any cigarettes or less than 20 cigarettes per day. Smokers are those who smoke 20 or more per day.

SOURCE: Borhani, N. O., et al. (*17*).

An analysis was made by Schor (*86*) of 181 adult males who died from coronary heart disease generally less than 2 years after receiving a periodic health examination. The results of this study and those of Doll and Hill suggest that sudden death from previously undetected coronary heart disease frequently occurs among cigarette smokers. If this is true, it may, in part, account for the small differentials in the prevalence of coronary heart disease between smokers and nonsmokers observed in some morbidity prevalence surveys. As will be described in the following section, longitudinal, prospective morbidity studies also show that smokers are more likely to die from sudden attacks of coronary heart disease.

CORONARY HEART DISEASE MORBIDITY*

In chapter 11 of the 1964 Surgeon General's Report, several prospective studies on the incidence of coronary heart disease (*24, 31, 78, 88*) established that smokers were subject to higher rates than nonsmokers. The relationship was reported to be more marked under 50 years of age than among older persons and appeared to be associated with myocardial infarction but not with angina pectoris. Since the 1964 report, recent findings from large-scale, on-going prospective studies have been reported, providing additional insight on the interaction between smoking and other important coronary heart disease risk factors. Current findings are summarized in the following pages including tables 7 to 13. Whenever possible, data are shown separately for findings related to angina pectoris and those pertaining to myocardial infarction, including sudden death attributed to coronary heart disease. Higgins (*50*) has drawn attention to the fact that "many factors may influence or be affected by smoking habits, and obscure those differences between smokers and nonsmokers which are directly related to the use of tobacco." In her review of the literature, Higgins identified differences between smokers and nonsmokers in genetically

*Also may include mortality data in this presentation.

determined qualities (*23*), in physique (*77, 93*), in personality (*37, 47, 48, 65, 68, 69*), and in social, cultural, religious, and economic characteristics (*46, 49, 68, 84*).

Age

The effect of age on the incidence of coronary heart disease with regard to cigarette smoking is shown in table 7 based on recent data from the Framingham Study as yet unpublished.

TABLE 7.—*Incidence rates and morbidity ratios for coronary heart disease by age and smoking status of men 12-year experience, Framingham, Mass.*

Age	Incidence rates per 1,000		Excess rates per 1,000	Morbidity ratio	
	Non-smokers	Smokers	Smokers minus non-smokers	Non-smokers	Smokers
35 to 44	1.4	4.1	2.7	1.0	2.9
45 to 54	4.6	11.1	6.5	1.0	2.4
55 to 64	16.2	25.4	9.2	1.0	1.6

SOURCE: U.S. Public Health Service, Framingham Study (*96*). (Updated 1967)

When the incidence rate of coronary heart disease among male nonsmokers between 35–44 years of age is compared with that among older nonsmokers, the rate is seen to triple every 10 years. This marked increase in incidence among nonsmokers reflects the effect of other important risk factors and perhaps accounts for the decrease in morbidity ratio as age advances. The independent effect of smoking on the incidence of coronary heart disease is believed to be more appropriately represented by the excess morbidity rates, which increase from 2.7 per 1,000 smokers in the age group 35–44 to 9.2 per 1,000 smokers 55–64 years of age.

High Blood Pressure

Although the inhalation of cigarette smoke is frequently accompanied by acute transient elevations in blood pressure, habitual smokers tend to have lower blood pressures than do nonsmokers (*48*). But, given the presence of high blood pressure in an individual, smoking acts as an additional risk factor for the development of coronary heart disease (*17, 28, 29, 30, 53, 55, 95, 96*). Both the independent and the combined effect of cigarette smoking is clearly shown in table 8 derived from the experience of the Framingham and Albany studies (*30*).

TABLE 8.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of systolic blood pressure*

Systolic blood pressure	Nonsmokers of cigarettes	Cigarette smokers
Under 130 mm. Hg	1.0	2.1
130 mm. Hg and over	1.8	3.8

SOURCE: 10-year Framingham and 8-year Albany experience (*30*).

High Serum Cholesterol

It is not now conclusively known if cigarette smoking by itself can cause increases in serum cholesterol. Dietary influences as well as endogenous production and elimination of cholesterol must be evaluated in greater detail with simultaneous analysis of the roles of other risk factors, including smoking. One study of a small population of twins in Sweden, as reported by Lundman (*67*), suggests that smoking monozygotic twins tend to have lower cholesterol levels than their nonsmoking control twins, although the differences are not statistically significant. Other studies suggest that smokers generally have higher serum cholesterol than nonsmokers (*13*, *67*, *88*). However, given the presence of high serum cholesterol, smoking increases the risk of coronary heart disease (*95*,*96*).

The independent any synergistic effect of cigarette smoking is demonstrated by the data in table 9 derived from the combined experience of the Framingham and Albany studies (*30*).

TABLE 9.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of serum cholesterol*

Serum cholesterol level	Nonsmokers of cigarettes	Cigarette smokers
Low [1]	1.0	1.8
High [1]	2.0	4.5

[1] "Low" is below median, "high" is above median value of serum chloesterol.
SOURCE: 10-year Framingham and 8-year Albany experience (*30*).

Pulmonary Function

The acute effects of cigarette smoking upon pulmonary function are expressed mainly through increase in airway resistance. The differences in pulmonary function between smokers and nonsmokers appear to be greater than can be accounted for by acute effects from a recently smoked cigarette (*50*, *91*). The relationship of coronary heart disease to lowered pulmonary function as reflected by low vital capacity and cigarette smoking is observed in the data published by the Na-

tional Institutes of Health based on the 12-year experience in Framingham (*96*). Morbidity ratios derived from this publication are shown in table 10.

TABLE 10.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to level of vital capacity*

Vital capacity	Nonsmokers of cigarettes	Cigarette smokers
Under 3 liters	1.0	1.7
3 liters or more	1.7	2.4

SOURCE: The Framingham heart study. (*96*).

Here again, the independent and combined effects of cigarette smoking are observed.

Physical Inactivity

A physically inactive or sedentary individual seems to run a higher risk of developing coronary heart disease (*39*, *40*, *41*, *76*). Spain (*88*) reported that, in his prospective study of 3,000 men "* * * the relationship of occupational physical activity to smoking habits revealed that one of six sedentary workers were heavy smokers and one of five strenuous workers were heavy smokers." Weinblatt, in reporting the experience of the Health Insurance Plan of Greater New York (*100*) also found that a higher proportion (41.9 versus 36.0 percent) of cigarette smokers were classified in the "most active" physical activity category.

The independent and the combined effects between cigarette smoking and physical activity are shown in table 11. The morbidity ratios for myocardial infarctions are derived from published data.

TABLE 11.—*Age-adjusted morbidity ratios for myocardial infarctions among smokers and nonsmokers according to physical activity level*

Physical activity	Nonsmokers of cigarettes	Cigarette smokers
Most active	1.0	2.6
Least active	2.4	3.4

SOURCE: Weinblatt, E. (*100*).

Socioenvironmental Stress

Since 1955, research on socioenvironmental stress in relation to coronary heart disease has increased greatly (*83*, *92*). Among the factors studied that indicate a strong association with coronary heart disease incidence and prevalence is sociocultural mobility, that is, moving from one social setting to another. The interaction of this factor and

cigarette smoking has been reported by Syme (*90, 91*) in both an urban and rural setting. Apparently in both areas cigarette smokers were more culturally mobile than nonsmokers. The independent effect of cigarette smoking on the incidence of coronary heart disease is shown in the morbidity ratios in table 12 derived from the North Dakota study (*91*).

TABLE 12.—*Age-adjusted morbidity ratios for coronary heart disease among smokers and nonsmokers according to sociocultural mobility status*

Sociocultural status	Never smoked cigarettes	Current and former cigarette smokers
Stable	1. 0	1. 5
Highly mobile	2. 3	3. 2

SOURCE: North Dakota study. (*91*)

Personality Type

Various investigators have long suspected a possible pathogenetic role of the central nervous system in coronary heart disease (*35*). In a series of reports, Rosenman (*81, 82*) and Jenkins (*51*) have described a personality pattern or overt emotional complex which, while associated with other known risk factors, appears to predict coronary heart disease more effectively than do other risk factors. This emotional complex, "which they have termed Behavior Pattern Type A, is composed of an enhanced competitiveness, drive, aggressiveness and hostility, and an excessive sense of time urgency." Recent unpublished data based upon prospective observation of more than 3,000 men for a 4½-year period (*51*) discloses that smokers have a higher percentage (54 versus 47 percent) of type A persons among them. Moreover, the incidence of coronary heart disease is shown to be related independently to both smoking status and personality type. Morbidity ratios, derived from the incidence data, are shown in table 13 which clearly demonstrates the independent effects of cigarette smoking and its interaction with personality characteristics.

TABLE 13.—*Morbidity ratios of cigarette smokers as compared to nonsmokers by personality type*

Personality type	Nonsmokers of cigarettes	Cigarette smokers
Behavior type B	1. 0	2. 0
Behavior type A	2. 5	4. 4

SOURCE: Unpublished data from Western Collaborative Group Study, San Francisco, Calif. (*82*).

Multiple-Risk Factors

The method of analysis traditionally employed by epidemiologists, that of the comparison of rates for multiple cross-classifications of the data, generally requires a large study population at relatively high incidence of significant events. Since coronary heart disease incidence rates are low and study populations are necessarily small because of practical and practicable limitations, definitive analysis of the independence and interaction between risk factors have generally been restricted to two factors at a time. Truett (*95*) applied a multiple logistic function proposed by Cornfield to investigate the independent effect on the incidence of coronary heart disease of seven risk factors: Age, serum cholesterol, systolic blood pressure, relative weight, hemoglobin, cigarettes per day, and ECG abnormalities. The method was used in the analysis of data compiled in the Framingham study during a 12-year period. A discriminant function coefficient was computed for each risk factor. These coefficients represent the relative importance of each factor with respect to the other six factors in the development of coronary heart disease. While theoretical considerations underlying the logistic risk function are not fully satisfied by the actual data, the approximation given by the function to observed rates is very good.

Consequently, Truett and Cornfield believe that the present computations permit the conclusion that "the most important risk factors, aside from age itself, are cholesterol, cigarette smoking, ECG abnormality, and blood pressure" (*95*).

Manifestation of Coronary Heart Disease

Coronary heart disease is essentially comprised of three major manifestations or subcategories:

1. Fatal myocardial infarctions, including sudden deaths attributed to coronary heart disease;
2. Nonfatal myocardial infarction; and
3. Angina pectoris.

Generally, investigators in their analysis of the relationship of risk factors to the incidence of coronary heart disease have not subdivided the observed coronary events into the three major subcategories primarily because the paucity of events in each category did not permit definitive conclusions on any differences observed. However, the pooling of data from some of the larger prospective studies holds promise of a more complete analysis of the independent and synergistic effects of each risk factor on each of the subcategories of coronary disease. Findings from these analyses might provide some insights into the underlying pathophysiological mechanisms through which a risk factor operates. The pooled data from the Albany and Framingham studies and data from the HIP study include the observed associations of

cigarette smoking with each of the three major manifestations. Morbidity ratios have been derived from these studies and are presented in table 14.

TABLE 14.—*Age-adjusted morbidity ratios for subcategories of coronary heart disease among smokers and nonsmokers*

Disease category	Framingham-Albany		Health insurance plan	
	Non-smokers of cigarettes	Cigarette smokers	Non-smokers of cigarettes	Cigarette smokers
Fatal myocardial infarction	1.0	2.4	1.0	2.1
Non-fatal myocardial infarction	1.0	2.3	1.0	1.8
Angina pectoris	1.0	1.1	1.0	1.7

SOURCE: Second Report of the Combined Experience from Albany and Framingham Studies (*50*). Unpublished Data from Health Insurance Plan Study (*100*).

The association of cigarette smoking to angina pectoris is not a consistent one. A clear-cut association was found in the Health Insurance Plan Study (ratio of 1.7); a similar association is also found in unpublished data from Framingham considered separately. However, no association between cigarette smoking and the incidence of angina pectoris was found in the Albany experience. Cederlof (*19*), in his analysis of prevalence data on angina pectoris obtained by questionnaire, found no statistically significant difference in prevalence rates between 453 monozygotic twin pairs with dissimilar smoking habits. In a larger study of about 9,000 persons from the twin register where genetic factors were uncontrolled, Cederlof (*19*, *20*) did find a significantly higher prevalence of angina pectoris among smokers than nonsmokers, particularly in men (ratio of 1.6) (*67*).

Friedman (*42*) and Epstein (*36*) have clearly described the inherent biases in prevalence studies which may lead to findings of risk gradients that are different from those obtained in prospective incidence studies. One of these limitations is that fatal cases are underrepresented in a prevalence survey. Thus, since it appears that cigarette smoking is more closely related to the incidence of fatal myocardial infarctions than to other forms of coronary heart disease, it is expected that morbidity ratios derived from prevalence surveys would be lower than those computed from incidence data. With these restrictions in mind, Russek (*83*) in a survey of 12,000 men in 14 occupational groups found that the morbidity ratio of coronary heart disease prevalence among cigarette smokers was as high as 1.8. In contrast, in a study of 77 identical and 89 fraternal twins in Sweden, comparing smokers with their respective nonsmoking twins, Lundman (*67*) reported no excess prevalence of overt or silent coronary heart disease. However,

the prevalence of these conditions, as Lundman concluded, "was too low to permit of definitive conclusions."

Cardiovascular Response to Smoking and/or Nicotine

As noted in the Surgeon General's 1964 Report, nicotine has definite physiologic effects on the cardiovascular system of experimental animals and of man. These include increases in heart rate, systemic arterial pressure, cardiac output, stroke volume, and velocity of myocardial contraction, all resulting in an increased myocardial tissue oxygen demand (*16*). Coronary blood flow studies will be reported in the next section under a separate subheading. These effects parallel those observed with catecholamines (epinephrine and norepinephrine). The effects can be blocked by the injection of tetraethylammonium chloride and markedly reduced by adrenalectomy (*22*). Nicotine has been repeatedly shown to release endogenous catecholamines (*57*, *58*, *59*, *60*, *102*). However, the mechanism by which nicotine affects the cardiovascular system is more complex than the release of catecholamines from the adrenal medulla. Direct and indirect (via the carotid body and other chemoreceptors) stimulation of the vasomotor center, stimulation of sympathetic ganglia, release of norepinephrine from local stores, and release of antidiuretic hormone are included among other postulated mechanisms of action involved in nicotine's effect on the cardiovascular system (*16*, *63*, *85*).

Coronary Blood Flow in Normal Subjects

The action of smoking and/or nicotine on the coronary blood flow of normal human subjects has not yet been definitively established, but apparently normal subjects can increase their coronary blood flows sufficiently to maintain a compensatory blood supply to the myocardium despite the increased myocardial tissue demand for oxygen caused by cigarette smoking. Earlier findings of increased coronary blood flow in normal men, in response to cigarette smoking (*11*), were not reproduced in a more recent study (*16*). In this latter study, although a trend towards a slight increase in coronary blood flow was observed in the particular normal persons studied, it was not significant.

Direct injection of nicotine into the left coronary artery of dogs under conditions of constant flow rate resulted in increased coronary vascular resistance (*38*, *64*). This response could be reduced by vagal nerve stimulation or prior adminstration of acetylcholine; an immediate increase in cardiac contractile force was also observed that could be similarly reduced. It was concluded that these responses to nicotine resulted from sympathetic nervous system activity or from the release of catecholamines by myocardial chromaffin tissue (*64*).

Blood from the smoke-exposed lung tissue of dogs, directly perfused

into the coronary artery, failed to increase coronary resistance (*38*). This effect was thought to be secondary to that of histamine, known to act as a coronary vasodilator, which apparently is released from the lung tissue of dogs during their exposure to smoke (*8*).

When blood from the smoke-exposed lung was perfused through the systemic circulation of dogs while the coronaries were being perfused with non-smoke-exposed blood, the typical release of catecholamines occurred with many of the usual effects on cardiovascular parameters except that the coronary vascular resistance increased under these experimental conditions, apparently due to the increased activity of the sympathetic nervous system (*38*).

Since it is well known that exposing dogs to cigarette smoke without isolating and separately perfusing the coronary circulation normally results in an increase of the coronary blood flow (*38*), the manipulation of experimental conditions as described suggests that there is a masking effect by the catecholamines on nicotine's direct action on the coronary circulation (*38*).

These studies may relate, by analogy, to humans and indicate that smoking, in "normal" individuals, may produce at least two actions that can affect coronary blood flow: (1) a decrease in coronary blood flow by a possible direct action of nicotine on the coronary circulation (demonstrated in dogs), and (2) an increase in coronary blood flow as the usual resultant of varying responses to the intermediating action of catecholamines and other physiologic processes (demonstrated in both animals and humans).

Coronary Blood Flow in Subjects with Coronary Heart Disease

The effect of cigarette smoking on coronary blood flow was studied in patients with coronary heart disease (*79*). As was seen in normal subjects, significant increases in heart rate, arterial pressure, and cardiac output were noted. In contrast to the normal individuals studied, patients with coronary heart disease distinctly showed a much less significant compensatory increase in their coronary blood flows. These results were confirmed by a later study (*16*), using the Rubidium 84 method to estimate coronary blood flow. This study also showed that in the coronary patients studied, there was no adequate compensatory increase in coronary blood flow to meet the increased myocardial tissue demand for oxygen. Coronary blood flow apparently decreased as a result of cigarette smoking, in this particular study group of coronary patients. Although the decreases noted were not marked, they were statistically significant, and indicated that a difference existed between these coronary patients as compared to the normal subjects studied.

A difference in the coronary blood flow response to nitroglycerine has also been demonstrated in normal subjects compared to subjects with coronary heart disease. This was shown in studies using the

nitrous oxide (*18*, *44*) and the Rubidium 84 (*15*) methods to measure coronary blood flow. In response to nitroglycerine the normal individuals generally increased their coronary blood flow significantly, but the coronary patients generally did not.

Animal studies have also demonstrated the decreased ability of atherosclerotic coronary arteries to increase coronary blood flow, as compared to the coronary arteries in normal animals (*94*). Dogs with experimentally produced coronary artery insufficiency also show this decreased ability (*12*). Similar differences between animals with normal coronary arteries as compared to atherosclerotic coronary arteries have been demonstrated in response to ergonovine (*80*).

The above studies indicate that the effect of nicotine upon the cardiovascular system, mediated in part by the action of released catecholamines, is generally to increase heart rate and cardiac output, and to raise systemic arterial pressure temporarily. Findings concerning the effect of nicotine on coronary blood flow are presently thought to be largely due to the indirect effects of nicotine upon the cardiovascular system. Other animal studies indicate that there may be a direct action of nicotine on the coronary vasculature to increase coronary vascular resistance, thus tending to reduce coronary blood flow. There are no human studies on the direct action of nicotine by itself on the coronary vasculature; such studies, involving the direct injection of nicotine into diseased human coronary arteries, might be dangerous. Normal individuals apparently can increase their coronary blood flows to compensate for the increased myocardial tissue oxygen demand, but apparently some patients with coronary heart disease cannot, as shown by their response to smoking.

Thus some patients with coronary heart disease may be at a particular disadvantage when smoking and under other stresses since their coronary arteries apparently cannot dilate to supply blood flow adequate to meet the increased oxygen demand associated with nicotine-induced catecholamine release. The interaction of the above effect with recent findings concerning carbon monoxide, described in the next section, may be especially important in those individuals with coronary heart disease. The present studies indicate that the effect of cigarette smoking on coronary blood flow, in the presence of preexisting coronary heart disease, may, in part, contribute to the increased incidence of acute myocardial infarctions that have been observed to be associated with cigarette smoking. No relationship between the smoking effect on coronary blood flow and the pathogenesis of coronary atherosclerosis per se is presently suggested. Additional research is needed.

Carbon Monoxide Effect

The gaseous phase of cigarette smoke contains about 4 percent carbon monoxide. This quantity can increase the levels of carboxyhemo-

globin saturation of cigarette smokers from 2 percent to 10 percent (*21*). The average nonsmoker, depending on environmental exposure, usually has less than 2 percent carboxyhemoglobin saturation (*10*). Since smokers of one pack or more a day may have chronically elevated carboxyhemoglobin levels of more than 4 percent (*9*), there may be appreciable differences in the carboxyhemoglobin levels between some heavy cigarette smokers and nonsmokers.

In addition to displacing oxyhemoglobin, carbon monoxide effects a shift in the oxygen-hemoglobin dissociation curve (*2*, *3*, *4* *5*, *6*). This may result in a decreased release of oxygen at the tissue level. A series of studies (*61*, *62*) has been performed on young adults to analyze the effect of cigarette smoking on carboxyhemoglobin levels, and the consequent effect on some parameters of cardiopulmonary function. An increased post exercise oxygen debt was observed after cigarette smoking as compared to controls. This, in part, may reflect not only ventilatory disturbances but also a decreased supply of oxygen in the blood due to the carbon monoxide effect, resulting in less available oxygen to meet the increased tissue demand. Similar post-exercise oxygen debts have been noted after inhalation of enough carbon monoxide to produce comparable blood levels of carboxyhemoglobin (*21*).

The consequence of the smoking/carbon monoxide effect appears to be especially important in the myocardium where relatively more oxygen is normally extracted from the coronary circulation as compared to other organ systems. (Coronary venous blood usually has an oxygen saturation of less than 25 percent, whereas blood leaving some other organs is about 75 percent saturated with oxygen (*45*).)

Dogs were exposed to carbon monoxide to elevate their carboxyhemoglobin saturation levels (*9*). In response to inhalation of carbon monoxide there was an increase in coronary blood flow but a decrease in coronary arterial-venous oxygen differences. Patients with coronary heart disease were also studied following inhalation of enough carbon monoxide to elevate their carboxyhemoglobin saturation levels to the range of 5 to 12 percent (*9*). In response to carbon monoxide there was generally an increase in the cardiac output and the coronary blood flow in most of the patients. While the systemic arterial-venous oxygen differences varied, either increasing or decreasing, the coronary arterial-venous oxygen differences decreased, indicating a decreased oxygen extraction by the myocardial tissue despite the myocardium's increased demand for oxygen. These decreases in myocardial oxygen extraction are related to increases in the carboxyhemoglobin saturation levels. It was observed that some patients evidently could compensate by increasing their coronary blood flows adequately to supply the myocardial tissue with sufficient oxygen, as indicated by a rise in myocardial oxygen uptake in these individuals. However, the other

patients with coronary heart disease, evidently more severe, could not increase their coronary blood flow rate enough to compensate for the decreased oxygen carried by the blood. This latter group of patients, even though they had increased cardiac output, had less significant increases of coronary blood flow than those noted in the first group of patients. The coronary arterial-venous oxygen differences and the myocardial tissue oxygen uptakes both decreased, indicating that the myocardial tissue oxygen demand was not being met entirely.

The reduction in the amount of oxygen available to the myocardial tissue caused by the absorption of carbon monoxide from tobacco smoke may be especially critical in persons with pre-existing coronary heart disease, especially when they cannot significantly increase coronary blood flow to compensate for increased myocardial tissue oxygen demand. The carbon monoxide effect may, in part, contribute to the increased incidence of myocardial infarctions that occur in cigarette smokers. Additional research is needed.

Studies on In Vitro *Thrombus Formation*

Recent studies have indicated that cigarette smoking may accelerate thrombus formation of human blood *in vitro*. Platelet adhesiveness, as measured by *in vitro* tests, also appears to be increased by cigarette smoking (*1*, *43*, *71*, *87*). Other studies, comparing smokers with nonsmokers, indicate that the platelet survival time of the smokers is shortened (*73*) and the platelet turnover rate is increased (*72*). Studies of animals show there is also an increased tendency for the platelets to adhere to the vascular endothelium.

Platelet adhesiveness is reported to be increased in *in vitro* studies using the Chandler rotating loop (*32*, *33*, *34*); these studies generally show a consistent acceleration of the rate of thrombus formation. Other *in vitro* tests show changes in thrombus formation and some parameters of coagulation as a result of smoking (*56*, *66*, *87*). However, problems in experimental design and the multiplicity of tests used, measuring either the same or overlapping portions of the complicated coagulation process with varying results, cause difficulty in evaluating these results (*71*).

The mechanism of changes in characteristics of the platelets in smokers is being investigated, but there are indications that the release of catecholamines, especially epinephrine, caused by the absorption of nicotine during smoking may be intimately involved (*71*, *72*). In small doses, epinephrine has been shown to promote thrombus formation and coagulation, but in large doses it inhibits these processes. Changes in the electrical charge of the platelet membrane have also been implicated in increasing platelet adhesiveness (*101*), increasing adherence to the vascular endothelium, and accelerating thrombus formation as measured by the Chandler loop method. Some of the alterations in thrombus formation may be mediated by an interaction

with serum-free fatty acids and cholesterol (*70*) but current evidence suggests that inhalation of cigarette smoke acts primarily through other independent factors (*101*). Thus, cigarette smoking may cause an acceleration of the *in vitro* thrombus formation of human blood. It is reasonable to suspect that cigarette smoking, in part by affecting the thrombus-forming process in human blood, may account for some of the excess coronary heart disease deaths that occur in cigarette smokers, especially some of the deaths certified as "acute coronary thrombosis." Further research is necessary before any definite conclusion can be made.

Autopsy Studies

The two most significant pathological studies of the relationship of smoking history to atherosclerotic changes in human coronary arteries have been reported by Auerbach and Strong. Auerbach (*7*) studied 1,372 males for whom a smoking history was available and who had died of causes other than coronary heart disease. He found that the percentage of men with an advanced degree of coronary atherosclerosis was higher among cigarette smokers than among nonsmokers, and that the percentage increased with amount of cigarette smoking. Both among smokers and nonsmokers the percentage of men with advanced coronary atherosclerosis also increased with age. This relationship held up even when the following were excluded: men with a history of diabetes, men who had died of any type of heart disease, and men whose hearts weighed 400 gm. or more. A matched set analysis was also carried out (reincluding some diabetics and heart disease deaths) and again the percentage of men with advanced coronary atherosclerosis was less among nonsmokers than among men who had been current cigarette smokers, and this percentage increased with the amount smoked.

Strong (*89*) in a study of coronary arteries from 645 autopsied males, 20 to 64 years of age, excluded patients with diseases he thought to be associated with smoking (emphysema, lung cancer, etc.), or with coronary heart disease (myocardial infarction, hypertension, diabetes, stroke, etc.). He found that the mean percent of coronary intimal surface occupied by raised atherosclerotic lesions was approximately twice as great in heavy smokers (25+ cigarettes/day), and about one-third greater in light smokers (less than 25/day), than in nonsmokers. Calcified lesions and mean coronary wall thickness measured radiographically were on the average highest in heavy smokers and lowest in nonsmokers. Differences among these smoking categories were generally greatest at younger ages.

These autopsy studies suggest that smoking, in addition to the acute immediate effect associated with the act of smoking, has a chronic effect leading to advanced degrees of atherogenesis. However, these findings may, in part, reflect the differences noted between

smokers (*7, 89*), particularly heavy smokers, and nonsmokers in regard to greater obesity, higher dietary fat intake, and higher serum cholesterol levels. Further analyses of autopsy series are needed to determine the independent effects of cigarette smoking on atherogenesis.

SMOKING AND CEREBROVASCULAR DISEASE

An increasing amount of evidence has accumulated in the past few years relating the development of clinical cerebrovascular disease to cigarette smoking. Most of this information has come from the prospective mortality studies.

Hammond has reported the following data from his large prospective study (*47*), noted in table 15.

TABLE 15.—*Cerebral vascular lesions. Age-standardized death rates, by type of smoking (lifetime history) and age at start of study*

	Age			
	45-54	55-64	65-74	75-84
	CVL death rates per 100,000 person-years			
MEN				
Never smoked regularly	28	92	349	1, 358
Pipe, cigar	25	100	369	1, 371
Cigarette and other	28	129	361	990
Cigarette only	42	130	477	1, 168
Total	35	116	391	1, 272
WOMEN				
Never smoked regularly	18	57	228	1, 082
Cigarette	38	88	315	1, 277
Total	25	64	238	1, 091
	CVL mortality ratios			
MEN				
Never smoked regularly	1. 00	1. 00	1. 00	1. 00
Pipe, cigar	. 89	1. 09	1. 06	1. 01
Cigarette and other	1. 00	1. 40	1. 03	. 73
Cigarette only	1. 50	1. 41	1. 37	. 86
WOMEN				
Never smoked regularly	1. 00	1. 00	1. 00	1. 00
Cigarette	2. 11	1. 54	1. 38	1. 18

SOURCE: E. C. Hammond (47).

Between the ages of 45 and 74 the death rates from stroke for male smokers were 37 to 50 percent higher than those for male nonsmokers of comparable age. In female smokers the death rates from stroke were 38 to 111 percent greater than those for nonsmokers. Above the age of 74 the differences between the two groups were much less.

The data in Table 16 concerning smoking and death rates from stroke are derived from the U.S. veterans study (*52*).

TABLE 16.—*Mortality ratios and death rates for stroke as underlying cause among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.51	1.42	1.70	1.59
Death rates:					
Age 55 to 64	59	92	112	125	130
Age 65 to 74	280	323	312	382	502

SOURCE: U.S. veterans study (*52*).

When stroke was certified as the principal cause of death, the death rates for smokers were higher than for nonsmokers; however, no pronounced increase was noted in the mortality ratios as the degree of smoking increased. The death rates from stroke for all ages was 59 percent higher in heavy smokers (40 or more cigarettes) than in nonsmokers.

TABLE 17.—*Mortality ratios and death rates for stroke as the underlying or contributory diagnosis among current smokers of cigarettes only*

	Quantity of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio (all ages)	1.00	1.45	1.45	1.75	1.83
Death rates:					
Age 55 to 64	101	152	174	195	216
Age 65 to 74	424	514	520	616	724

SOURCE: U.S. veterans study (*52*).

Stroke, listed as either the underlying or contributory cause of death on the death certificate, was also associated with progressively increasing mortality ratios and death rates as the extent of smoking increased. Heavy smokers here had an 83 percent greater mortality from stroke than nonsmokers.

Mortality data by underlying cause of death may often be misleading, particularly when stroke is concerned. Many stroke patients have

concomitant coronary heart disease, or may develop pneumonia and other complications that may hasten death. The death certificate may carry stroke as the underlying cause or as the contributory cause of death, depending upon the interpretation of the physician at the time. The important addition of these data is that smoking is associated with a higher mortality from stroke, whether the stroke is recorded as either the underlying cause or as the contributory cause of death.

These two studies indicate that smoking may be associated with a higher mortality from stroke in the relatively younger age groups (under age 74). More than one-half the strokes that occur each year are in the group above age 75 and in this group there is no evidence relating smoking to cerebrovascular disease.

Another large study has been conducted analyzing the mortality of 50,000 former students who entered Harvard University or the University of Pennsylvania during the years 1916–50 (*74*, *75*, *76*). From this population 171 deaths from cerebrovascular accidents have been identified. A review of the medical records from their college years has been carried out, and selected factors were correlated with the later occurrence of stroke. Seven precursive "risk factors" present at the time of college attendance have been defined: Cigarette smoking, high blood pressure, excess body weight, short stature, a history of early parental death, a history of nonparticipation in college sports, and a history of "heart consciousness" (also shown to be correlated with coronary heart disease). Cigarette smoking and a history of early parental death were more strongly correlated with thrombotic stroke than with hemorrhagic stroke. Students who smoked more than 10 cigarettes daily were at twice the risk of having a fatal stroke than were those who smoked less or not at all.

In 1965 the Framingham study (*54*) reported that while an excess development of thrombotic brain infarction appeared to be associated with cigarette smoking, statistically significant differences could not be demonstrated with the small number of cases available at that time. More recent data from Framingham indicates that cigarette smoking increases the risk of stroke in males. The relatively small number of women smokers had too few strokes for adequate analysis.

The new epidemiological evidence, then, indicates that cigarette smoking may be more closely associated with cerebrovascular disease in the population between the ages of 45 and 74 years than was previously indicated. If cerebrovascular thrombosis (thrombotic brain infarction) accounts for this association, it is possible that some of the considerations of how cigarette smoking may produce coronary thrombosis also apply to the pathogenesis of cerebrovascular disease. Further research is essential to understand the relationships that exist between cigarette smoking and cerebrovascular disease.

Additional information on mortality data concerning aortic aneurysm has been provided by the U.S. veterans study (*52*) and the Hammond (*47*) studies, as noted in tables 18 and 19, respectively.

TABLE 18.—*Mortality ratios and age-standardized death rates for aortic aneurysm in U.S. veterans, current smokers of cigarettes only*

	Number of cigarettes smoked per day				
	0	1-9	10-20	21-39	40+
Mortality ratio	1. 00	2. 12	5. 53	5. 95	7. 26
DEATH RATES					
Age:					
55 to 64	6	13	27	43	44
65 to 74	25	57	123	157	221

SOURCE: U.S. veterans study (*52*).

TABLE 19.—*Mortality ratios and age-standardized death rates for aortic aneurysm*

	Age 45-64 years		Age 65-79 years	
	Females	Males	Females	Males
Mortality ratio	3. 89	2. 62	3. 33	4. 92
Death rates	[1] 4(*1*)	18(*7*)	43(*15*)	118(*24*)

[1] Numbers in parentheses indicate death rates of those who never smoked regularly.

SOURCE: Hammond, E. C. (*47*).

It is apparent that there is a close association between cigarette smoking and death caused by aortic aneurysms.

Thus, the additional evidence confirms the previously observed association between cigarette smoking and death due to nonsyphilitic aortic aneurysm.

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